

Formulation and Optimization of Fenofibrate Solid Lipid Nanoparticle- Based Gel for Enhanced Controlled Release and Transdermal Bioavailability

Muhimmatul Khoiriyah^{1*}, Ilham Kuncahyo², Jason Merari Perangirangin², TN Saifullah³, Iswandi², Annisa Fatmawati⁴, Adhi Gunawan⁴ and Salsabil Priladiya Rafida⁴

¹Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Alma Ata, Yogyakarta, Indonesia 55183

²Department of Faculty of Pharmacy, Universitas Setia Budi, Surakarta, Indonesia

³Department of Faculty of Pharmacy, Universitas Gajah Mada, Yogyakarta, Indonesia

⁴Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Alma Ata, Indonesia

Corresponding author

Muhimmatul Khoiriyah, Department of Pharmacy, Faculty of Medicine and Health Sciences, Universitas Alma Ata, Yogyakarta, Indonesia.

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ABSTRACT

Fenofibrate, a lipid-lowering drug, exhibits poor aqueous solubility and limited oral bioavailability, which consequently lead to inconsistent therapeutic efficacy. To address this limitation, this study developed a solid lipid nanoparticle (SLN)-based drug delivery system intended for transdermal application to enhance drug solubilization and provide controlled release. SLNs have emerged as a promising nanocarrier system owing to their ability to encapsulate lipophilic drugs within a solid lipid matrix and improve in vitro permeation characteristics.

This study aimed to optimize the formulation of fenofibrate-loaded SLNs, incorporate them into a gel base, and evaluate their in vitro release and transdermal diffusion behavior using Franz diffusion cells.

Fenofibrate-loaded SLNs were prepared using the hot homogenization–ultrasonication method, followed by optimization of lipid type, surfactant concentration, and process parameters. The optimized formulation was evaluated for particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency. The SLN gel was prepared using an appropriate gelling base and evaluated for in vitro drug release and diffusion using Franz diffusion cells.

The optimized SLN formulation exhibited a particle size of 182.4 ± 3.1 nm, a PDI of 0.268 ± 0.012 , a zeta potential of -28.7 ± 1.6 mV, and an entrapment efficiency of $88.9 \pm 2.4\%$. Incorporation of SLNs into the gel base significantly enhanced cumulative drug permeation, approximately 3.8-fold higher than the conventional fenofibrate gel, and demonstrated a sustained release profile consistent with non-Fickian diffusion kinetics.

The optimized SLN-based gel improved in vitro drug release and transdermal diffusion, indicating its potential as a promising nanocarrier system for controlled transdermal delivery of poorly water-soluble drugs. Further in vivo and skin-based studies are required to confirm its clinical applicability.

Keywords: Fenofibrate, Solid Lipid Nanoparticles, Formulation Optimization, Franz Diffusion, Controlled Release

Introduction

Fenofibrate, a fibric acid derivative and peroxisome proliferator-activated receptor alpha (PPAR- α) agonist, is widely prescribed for the management of hyperlipidemia and hypertriglyceridemia. However, its therapeutic effectiveness is hindered by extremely low aqueous solubility (approximately 162.5 $\mu\text{g/mL}$) and variable oral bioavailability, categorizing it as a Biopharmaceutical Classification System (BCS) Class

II drug poorly soluble but highly permeable [1,2]. These physicochemical characteristics result in slow dissolution rates and inconsistent systemic absorption, limiting therapeutic efficiency and patient outcomes [3]. Therefore, the persistent challenge in fenofibrate formulation lies in its poor solubility and limited bioavailability, underscoring the urgent need for advanced delivery systems capable of enhancing its dissolution, absorption, and overall therapeutic performance.

Solid lipid nanoparticles (SLNs) have emerged as a promising and biocompatible nanocarrier platform capable of addressing

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such limitations. Comprising physiologically acceptable solid lipids stabilized by surfactants, SLNs provide a structured matrix for efficient drug encapsulation, controlled release, and improved chemical stability [4-6]. Their submicron particle size enhances the surface area, facilitates interaction with biological membranes, and supports sustained drug release across dermal and transdermal barriers [7-9]. Previous studies have demonstrated the capability of SLNs to enhance dissolution and dermal penetration of lipophilic drugs such as meloxicam, atorvastatin, and ramipril, as well as topical delivery of phytochemicals and other bioactive compounds [10-15].

Our previous study published in Natural Sciences Engineering & Technology Journal, successfully formulated fenofibrate-loaded SLNs using high-shear homogenization with glyceryl monostearate (GMS) and Tween 40 [16]. The result show that particle sizes ranging from 490 to 2410 nm, polydispersity indices between 0.02 and 0.65, and entrapment efficiencies exceeding 70%, confirming the feasibility of SLN systems to enhance fenofibrate's physicochemical properties. However, that investigation primarily focused on preliminary characterization without statistical optimization or evaluation of transdermal delivery potential.

To advance this previous work, the present study employed systematic optimization using factorial design (Design Expert® software) to evaluate the influence of lipid and surfactant concentrations on key physicochemical parameters, including particle size, polydispersity index, and entrapment efficiency [17,18]. Furthermore, the optimized SLNs were incorporated into a hydrogel base containing hydroxypropyl methylcellulose (HPMC) to enhance suitability for transdermal application, enabling controlled release and improved skin permeation [2-19].

Therefore, this study aims to optimize the formulation of fenofibrate-loaded SLNs using a factorial design approach, incorporate the optimized nanoparticles into a topical hydrogel, and evaluate their in vitro release and diffusion behavior using Franz diffusion cells. This study represents a continuation of our previous research and seeks to establish a functional SLN-based gel formulation capable of improving the controlled release and transdermal bioavailability of fenofibrate [16].

Materials

Fenofibrate (≥99% purity) was used as the model lipophilic drug. Glyceryl monostearate (GMS) served as the solid lipid, while Tween 40 functioned as the nonionic surfactant. Hydroxypropyl methylcellulose (HPMC, 4000 cps) was employed as the gelling polymer. Glycerin, triethanolamine (TEA), and distilled water were used for gel preparation. All reagents were of analytical grade and used without further purification.

Instruments

Key analytical and processing instruments included an analytical balance (Precisa B220A, Switzerland), magnetic stirrer with hot plate (Thermo Scientific, USA), probe ultrasonicator (UP200St, Hielscher, Germany), particle size and zeta potential analyzer (Microtrac Nanotrac Wave II, USA), refrigerated centrifuge (Hettich Rotina 420R, Germany), and UV-Visible spectrophotometer (Shimadzu UV-1800, Japan). Franz diffusion

cells (PermeGear, USA) fitted with cellophane membranes (pore size 0.45 µm) were used for in vitro diffusion studies.

Preparation of Fenofibrate-Loaded Solid Lipid Nanoparticles (SLNs)

Fenofibrate-loaded SLNs were prepared using the hot homogenization-ultrasonication method with slight modifications [16]. Briefly, GMS was melted at 80 °C under magnetic stirring (700 rpm) for 15 min, followed by the addition of fenofibrate (0.12% w/w) until completely dissolved. Separately, Tween 40 was dissolved in an equal volume of hot distilled water (80 °C) and added dropwise to the lipid phase under continuous stirring to form a coarse pre-emulsion. The mixture was ultrasonicated for 15 min in pulse mode (10 s on/off, 55% amplitude) to obtain a fine nanoemulsion, which was allowed to cool at room temperature to promote lipid recrystallization and SLN formation.

Characterization of SLNs

Particle Size, PDI, and Zeta Potential: The mean particle size and polydispersity index (PDI) were determined by dynamic light scattering (DLS) using a Microtrac Nanotrac Wave II analyzer (refractive index = 3.33) at 25

- C. Zeta potential measurements were conducted with the same instrument to assess colloidal stability.

Entrapment Efficiency (EE%): Entrapment efficiency (EE%) was determined by centrifugation of SLN dispersions at 6000 rpm for 60 min. The amount of free (untrapped) fenofibrate in the supernatant was quantified spectrophotometrically at 286 nm. EE% was calculated using Equation (1):

$$EE(\%) = \frac{W_t - W_f}{W_t} \times 100$$

where W_t is the total drug content and W_f is the amount of free drug in the supernatant.

Optimization of SLN Formulation Using Design Expert®: A 2^2 full factorial design was constructed using Design Expert® version 12 (Stat-Ease Inc., USA) to evaluate the effects of formulation variables. Independent variables included GMS concentration (0.31–1.25% w/w) and Tween 40 concentration (1.33–2.00% w/w). Dependent variables were particle size, PDI, zeta potential, and EE%.

Experimental data were analyzed using analysis of variance (ANOVA) to determine model significance and interaction effects. Regression equations were generated for each response, and numerical optimization was performed to identify the most desirable formulation exhibiting minimum particle size and PDI, maximum EE%, and acceptable zeta potential.

The optimized formulation, containing 1.23% w/w GMS and 1.41% w/w Tween 40, achieved a desirability index of 1.0 and was prepared to validate model predictions.

Preparation of Fenofibrate SLN-Based Gel: The optimized SLN dispersion was incorporated into a hydrogel base consisting of HPMC (1% w/w), glycerin (10% w/w), and TEA (q.s. to pH 7.0). HPMC was dispersed in distilled water and allowed to hydrate for 1 h, followed by the addition of glycerin. The optimized

SLN dispersion was gradually incorporated under continuous stirring (1200 rpm) until uniform. TEA was then added dropwise to achieve a clear, homogeneous SLN-based gel. A control gel containing pure fenofibrate (equivalent drug concentration) was prepared following the same procedure, replacing the SLN dispersion with a fenofibrate solution.

In Vitro Diffusion Study Using Franz Diffusion Cells: The in vitro diffusion study was carried out using Franz diffusion cells fitted with cellophane membranes (pore size 0.45 µm). The receptor compartment (20 mL) was filled with phosphate buffer (pH 7.4), maintained at 37 ± 0.5 °C, and stirred at 250 rpm. Approximately 1 g of gel was uniformly applied to the donor compartment.

Aliquots (5 mL) were withdrawn at predetermined time intervals (15–300 min) and replaced with equal volumes of fresh buffer to maintain sink conditions. The samples were analyzed at 289 nm using a UV–Vis spectrophotometer. The cumulative amount of drug permeated per unit area (Q , µg/cm²) and steady-state flux (J , µg/cm²·h⁻¹) were calculated according to Fick's first law of diffusion (Equation 2):

$$J = \frac{dQ}{dt}$$

Table 1: Optimization Parameters and Experimental Ranges

Name	Goal	Low Limit	Upper Limit	Lower Weight	Upper Weight	Important
A : GMS	Is in range	0.31	1.25	1	1	3
B : Tween 40	Is in range	1.33	2	1	1	3
PSA	Is in range	490	1000	1	1	3
PDI	Is in range	0.01858	0.652	1	1	3
Zeta	Is in range	2.8	8.8	1	1	3
EE	Is in range	77.23	87.82	1	1	3

As can be seen from Table 1, numerical optimization indicated that the optimal formulation contained 1.227% GMS and 1.407% Tween 40, with a desirability value of 1.000. Model validation using one-sample t-tests revealed no significant differences between predicted and experimental data for particle size, PDI, zeta potential, and EE% ($p > 0.05$), confirming the reliability and robustness of the optimization process.

Table 2: Optimization Output and Desirability Results

Number	GMS	Tween	PSA	PDI	Zeta	EE	Desirability
1	0.583	1.807	956.715	0.198	80.842	1000	Selected

As shown, the desirability surface plots generated by Design Expert® 12 illustrate the interaction effects of glyceryl monostearate (GMS) and Tween 40 concentrations on the key response parameters particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency (EE%). The desirability function quantifies how well each response meets the predefined optimization criteria, with values ranging from 0 (undesirable) to 1 (highly desirable). A desirability value close to 1 indicates that the formulation simultaneously satisfies all target responses (Raissi & Farzani, 2009).

As visualized, the overlay contour plot clearly delineates the design space where the optimal conditions were achieved. The yellow-shaded region represents the feasible zone that meets the desired constraints for all dependent variables, while the gray-shaded region indicates non-optimal conditions. The optimal

The diffusion and permeation profiles of the optimized SLN gel were compared with those of the control gel.

Statistical Analysis: All experiments were conducted in triplicate, and data are expressed as mean $\pm$ standard deviation (SD). Statistical analyses were performed using Design Expert® 12 and SPSS version 24 (IBM Corp., USA). Predicted and experimental data were compared using one-sample t- tests at a 95% confidence level ($p < 0.05$).

Results and Discussion

Optimization of Fenofibrate SLNs Using Design Expert®:

As shown in Table 1, the optimization of fenofibrate-loaded SLNs was performed using Design Expert® software to evaluate the influence of lipid (GMS) and surfactant (Tween 40) concentrations on critical formulation parameters, including particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency (EE%). Statistical analysis confirmed that both independent variables had significant effects on all responses ($p < 0.05$), allowing the identification of the optimal formulation design space.

formulation was identified at 0.583% GMS and 1.807% Tween 40, which lies within the experimental range of GMS (0.31–1.25%) and Tween 40 (1.33–2.00%).

The selected formulation, having a desirability value of 1.000, demonstrates an ideal balance between particle size minimization, homogeneity (PDI), surface charge stability (zeta potential), and drug loading efficiency (EE%). These findings confirm that the applied factorial design effectively optimized the fenofibrate SLN formulation and established a statistically validated formulation space for further development.

Table 3: Formula Optimum

Fenofibrat (% w/w)	GMS (% w/w)	Tween 40 (% w/w)	Water (% w/w)
0.12	0.58	1.81	97.49

The optimized SLN characterization data were verified using a one-sample t-test in SPSS Version 24, comparing predicted values from Design Expert with experimental results for particle size, PDI, zeta potential, and entrapment efficiency. The verification confirmed no significant differences between predicted and experimental values, as indicated by p-values greater than 0.05.

Tabel 4: Hasil Analisis P-Value

Parameter	Predicted	Experimental	P-Value
PSA (nm)	956,715	182.4 ± 3.1	0.035
Polidispersi Index	0.198	0.268 ± 0.012	0.166
Zeta Potensila (mV)	4.594	-28.7 ± 1.6	0.056
Efisiensi Penjeraan (%)	80,842	88.9 ± 2.5	0.006

The one-sample t-test (two-tailed) conducted in SPSS Version 24 showed p-values greater than 0.05 for particle size, polydispersity index, zeta potential, and entrapment efficiency. This indicates that there were no statistically significant differences between the predicted values from Design Expert and the experimental results, confirming that the optimized SLN formulation closely matched the model predictions.

Preparation of Fenofibrate SLN-Based Gel: The optimized SLN dispersion was incorporated into a hydrogel containing 1% HPMC and 10% glycerin, adjusted to pH 7.0 with triethanolamine. The resulting gel was homogeneous, transparent, and viscous, suitable for transdermal application. This gel matrix provides mechanical stability, controlled release, and maintains the nanoscale advantages of SLNs (Bagde et al., 2019).

Determination of Maximum Wavelength (λ_{max}) of Fenofibrate: The maximum absorbance of fenofibrate in phosphate buffer pH 7.4 was determined to be 289 nm with an absorbance of 0.7447. This λ_{max} was used for subsequent measurement of drug permeation in the Franz diffusion study.

Calibration Curve of Fenofibrate: A linear regression between absorbance and concentration (ppm) was established as: $y = 0.0529x - 0.0096$, $R^2 = 0.9918$

where x is the concentration and y is the absorbance. The high correlation coefficient ($R^2 > 0.99$) indicates a reliable linear relationship suitable for quantifying drug permeation.

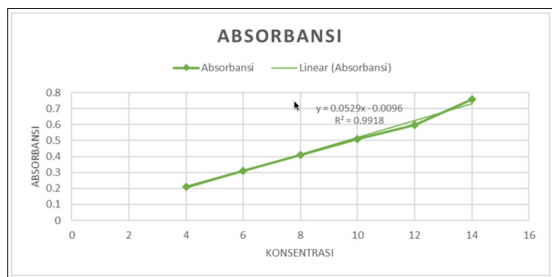


Figure 1: Linear Regression Calibration Curve of Fenofibrate in Phosphate Buffer pH 7.4

Franz Diffusion Study

Drug diffusion in the diffusion medium is a critical step prior to systemic absorption. Poorly water-soluble drugs, such as fenofibrate, generally exhibit low absorption (Shargel, 1988). This study aimed to evaluate the in vitro diffusion profile of Fenofibrate SLNs compared to pure fenofibrate using horizontal Franz diffusion cells with donor and receptor compartments. The cumulative amount of drug diffused was monitored over 5 hours.

The optimized SLN formulation was applied to the donor compartment, and diffusion was carried out at 2000 rpm for 5 hours. The Franz diffusion cell was chosen due to its well-defined surface area, which affects the rate of drug diffusion, and the receptor volume, which influences drug concentration detection.

The receptor compartment was filled with phosphate buffer pH 7.4, simulating physiological pH. A cellulose-based semi-permeable membrane was used to separate the donor and receptor compartments. Care was taken to eliminate air bubbles in the receptor compartment, as trapped air can prevent the drug from diffusing into the receptor solution.

Samples were withdrawn at predetermined time points, and the absorbance of each sample was measured using a double-beam UV-Vis spectrophotometer at 289 nm (λ_{max} obtained from the calibration curve). The measured absorbance values were then used to calculate cumulative drug permeation, percent penetration, and flux of the optimized Fenofibrate SLN formulation.

Table 5: Franz Diffusion Data of Fenofibrate Solid Lipid Nanoparticle Gel (F1)

Sample	Cumulative ($\mu\text{g}/\text{cm}^2$)	% Cumulative	Flux ($\mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$)
R1	78.854	0.742	472.182
R2	81.652	0.769	109.822
R3	129.799	1.222	147.813
Average	96.769	0.9115	243.272

Table 6: Franz Diffusion Data of Pure Fenofibrate Gel (F2)

Sample	Cumulative ($\mu\text{g}/\text{cm}^2$)	% Cumulative	Flux ($\mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$)
R1	30.388	0.286	149.56
R2	8.59	0.08	1.471
R3	51.558	0.485	32.415
Average	30.179	0.284	65.149

The average cumulative amount of the optimized Fenofibrate SLN gel that penetrated after 5 hours was $96.769 \mu\text{g}/\text{cm}^2$, with a percent penetration of 0.911% and a penetration flux of $243.272 \mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$. In contrast, the pure Fenofibrate gel showed lower cumulative permeation ($30.179 \mu\text{g}/\text{cm}^2$), percent penetration (0.284%), and flux ($65.149 \mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$).

These results demonstrate that the gel containing solid lipid nanoparticles (SLNs) significantly enhanced transdermal drug delivery compared to the conventional gel. The improvement is attributed to the nanoscale particle size of SLNs, which increases the surface area and facilitates more efficient penetration of the

active drug through the skin barrier.

The normality of the data was assessed using SPSS Version 24, and the results showed p-values > 0.05, indicating that the data were normally distributed (see Appendix: Test of Normality).

The combination of glyceryl monostearate (GMS) as the lipid matrix and Tween 40 as the surfactant in the SLN formulation enhances Fenofibrate solubility and contributes to the superior performance of the drug delivery system. Overall, the SLN gel provides controlled, sustained, and efficient transdermal delivery, outperforming the pure Fenofibrate gel in all measured parameters.

Study Limitations and Future Perspectives

Although the in vitro diffusion method employed in this study is appropriate for early-stage formulation screening, the use of cellophane membranes does not fully represent the complex physiological and barrier properties of human skin. Therefore, the diffusion data obtained should be interpreted as preliminary indicators rather than direct predictors of clinical transdermal performance.

Furthermore, this study was limited to in vitro diffusion evaluation, and no in vivo pharmacokinetic or safety assessments were conducted. Long-term physical stability, skin irritation potential, and large-scale production feasibility were also not investigated. Future studies should include ex vivo skin permeation models, in vivo pharmacokinetic evaluation, dermal irritation testing, and stability studies to comprehensively assess the clinical applicability and translational potential of the proposed SLN-based gel system.

Conclusion

This study successfully developed and optimized a fenofibrate-loaded Solid Lipid Nanoparticle (SLN) formulation using a high-speed homogenization technique. The optimized formulation validated by Design Expert® exhibited a mean particle size of 182.4 nm, a PDI of 0.268, a zeta potential of -28.7 mV, and an entrapment efficiency of 88.9%, confirming good colloidal stability and effective encapsulation of the lipophilic drug.

The in vitro Franz diffusion study demonstrated that the SLN-based gel achieved a cumulative permeation of 96.769 $\mu\text{g}/\text{cm}^2$ and a flux of 243.272 $\mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$, which were significantly higher than those of the pure fenofibrate gel (30.179 $\mu\text{g}/\text{cm}^2$ and 65.149 $\mu\text{g}/\text{cm}^2 \cdot \text{h}^{-1}$, respectively). These findings indicate that the SLN system enhanced in vitro transdermal drug permeation and provided a sustained, controlled-release profile, supporting its potential as an alternative delivery system for poorly water-soluble drugs.

Future studies are warranted to include in vivo pharmacokinetic evaluation, long-term stability testing, and skin irritation assessment to further validate the translational potential and clinical applicability of this SLN-based gel formulation.

Conflict of interest

The authors declare no conflict of interest.

Author's declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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